

Method to determine the spatial distribution of magnetic particles and magnetic particle administering compositions

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The present invention relates to a method to determine the spatial distribution of magnetic particles in an examination area of an object of examination and to magnetic particle administering compositions. The invention further relates to a magnetic particle composition having improved imaging properties, to administering compositions for administering magnetic particles into an examination area and to methods for the administering of magnetic particles.

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Imaging methods using magnetic particles as contrast agents are known. For example, in the MRI method (Magnetic Resonance Imaging), iron oxide is used as the contrast agent to influence relaxation times.

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DE 37 51 918 T2 describes a method to obtain an in-vivo image of an animal or human organ or tissue with the aid of nuclear magnetic resonance technology, in which an image-improving dose of nuclear magnetic resonance contrast agent, in the form of a superparamagnetic fluid, prepared in a specific manner, is used. The magnetic contrast agent influences the magnetic properties of the tissue under examination so that the irradiated protons evidence improved relaxation behaviour. Superparamagnetic and ferromagnetic substances make the magnetic resonance image appear darker due to the reduction of  $T_2$ . However, suitable contrast agents for nuclear spin tomography require extremely stable solutions to effectively increase the sensitivity of magnetic resonance measurement. The stability of suitable aqueous fluids of superparamagnetic iron oxides is frequently limited considerably by clumping due to magnetic forces of attraction between particles. DE 37 51 918 T2 proposes a four-stage method for the production of a stable superparamagnetic fluid comprising bivalent and trivalent metal salts. This method is very time and cost intensive and is therefore not necessarily suitable for standard examinations. Although the magnetic particles obtained with this method can be used to increase anatomical and physiological contrast, they are not generally suited to make the acquisition of parameters such as temperature and pH values using MRI technology more accurate and faster. In addition,

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nuclear spin tomography requires the use of very strong magnetic fields with high homogeneity. In general, superconducting coils are used together with liquid helium cooling. The nuclear spin tomography method is therefore always linked with a high equipment outlay.

5                   According to Chupp and Swanson, "Medical Imaging with Laser Polarized Noble Gases", Advances in Atomic, Molecular and Optical Physics, 45, 41 (2001), signals generated with magnetic resonance (MR) and nuclear magnetic resonance (NMR) methods can be amplified by several orders of magnitude when laser-irradiated polarized noble gases, particularly  $^3\text{He}$  and  $^{129}\text{Xe}$ , are introduced into the area of examination.  $^3\text{He}$  is particularly  
10                   suitable for lung imaging, while  $^{129}\text{Xe}$  is used, e.g. for the imaging of organs. The production of these noble gases polarized by laser radiation requires extensive equipment. In addition, it is difficult to produce large quantities of these polarized noble gases. Special measures must also be undertaken to ensure that the polarized noble gases are not contaminated by oxygen, even trace amounts, as this will essentially negate the signal amplifying effect.

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                  It is an object of the present invention to provide an imaging method using magnetic phenomena with which data, particularly data suitable for imaging, can be generated in a reproducible and precise manner with simple and cost-effective equipment  
20                   from the area of examination of an object of examination.

                  This object is achieved by providing a method to determine the spatial distribution of magnetic particles in an examination area of an object of examination with the following steps:

- a)           Generation of a magnetic field with a spatial distribution of the  
25           magnetic field strength such that the examination area consists of a first sub-area with lower magnetic field strength and a second sub-area with a higher magnetic field strength,
- b)           Change of the particularly relative spatial position of the two sub-areas in the area of examination or change of the magnetic field strength in the first sub-area so that the magnetization of the particles changes locally,
- 30           c)           Acquisition of signals that depend on the magnetization in the area of examination influenced by this change, and
- d)           Evaluation of said signals to obtain information about the change in spatial distribution and/or the movement of the magnetic particles in the area of examination, wherein the magnetic particles are introduced into and/or are present in the area of  
35           examination in a suspension, aerosol, in the form of a powder, especially diluted, with a

casing or, especially, a thin coating, present in at least one capsule, or coupled to cells, particularly white or red blood corpuscles, immune cells, tumor cells or stem cells, or to ingredients, medication, antibodies, transplants or living organisms, or in a preliminary stage, especially liquid, form. It is envisaged that an embodiment may include at least a repetition of steps b) to d).

Magnetic particles in a suspension are suitable for instance for intravenous injections, while magnetic particles in an aerosol are preferred for lung imaging or imaging of the breathing system. Magnetic particles in the form of a powder, especially a diluted powder, can be introduced either directly, or as a suspension or aerosol, into the area of examination. The encasing, or more particularly thin coating, of magnetic particles can prevent clumping or agglomeration of the particles during storage or introduction to, or while in, the area of examination. Preferably, temporary coatings or casings are used. Temporary coatings or casings can be made, e.g. of polysaccharides such as dextrane or viscous gels which, depending on the conditions in the area of examination, can partially or fully dissolve.

In a further embodiment, the magnetic particles are contained in a capsule or a coating and are brought in this form to the area of examination. Suitable capsule or coating materials are those that decompose and release the particles under certain conditions in the area of examination, e.g. at a specific pH value or temperature. In addition, a capsule material can be selected that dissolves when exposed to ultrasound or light.

A preferred embodiment of the method according to the invention is characterized in that the material used for encasing or coating the magnetic particles used can be degraded or dissolved thermally, chemically, biochemically, by means of electromagnetic radiation or ultrasound and/or mechanically. It may then be provided that the material for the encasing or coating comprises polysaccharides, starches, particularly dextrin or cyclodextrin, waxes, oils, fats, glycerin, gels or plastics, particularly thermoplastic polymers or their blends. Furthermore it may be provided that the magnetic particles have at least a partially coating or casing of at least one protein, polypeptide, antibody and/or organosilanes.

The coating of magnetic particles with biologically degradable materials, e.g. with dextrans and proteins, is described in DE 37 51 918 T2. Particle coatings with organic polymers are also described by Shen et al., J. Magn. Magn. Mater. 1999, 194, pages 37 ff., and by Del Gratta et al., Phys. Med. Biol. 1995, 40, pages 671 ff. The coating of magnetic particles can also be found in EP 186 616 A1.

Another aspect of the present invention also provides the introduction of magnetic particles coupled to cells, especially e.g. white or red blood corpuscles, immune cells, tumor cells and/or stem cells into the area of examination. The coupling of magnetic

particles to white blood corpuscles or immune cells enables the precise localization and imaging of sources of inflammation. The coupling of magnetic particles, especially magnetic nano-particles, to blood cells is described, e.g. by Groß et al., in "Jahrestagung der Deutschen Pharmazeutischen Gesellschaft", Münster, 2000. By coupling these particles to tumor cells or antibodies, it is possible to achieve very precise examination of tumour growth or propagation of tumors or metastasis formation. Administering forms are preferred where magnetic particles, coupled to medication, transplants or living organisms, are brought into and/or are present in the area of examination. In this manner it is possible to observe where the object coupled to the magnetic particles is transported to and by which route and speed. Living organisms marked with magnetic particles can comprise, e.g. bacteria or even insects, such as lice.

In a further embodiment of the present invention a precursor of magnetic particles is introduced to the area of examination. This has the advantage that not just magnetic particles present in solid form can be introduced to the area of examination, but that this introduction can take place with suitable solutions.

In particular, there is provided a method for administering a magnetic particle composition to an examination object, wherein the examination object is contacted with a first solution comprising ferrous and ferric ions and, before or after that, contacted with a second solution comprising a base to precipitate the magnetic particles in the examination area. A preferred embodiment provides that a precursor comprises a first aqueous solution containing  $\text{FeCl}_2$  and  $\text{FeCl}_3$ , and a second aqueous solution containing  $\text{NaOH}$ , is introduced to the area of examination where the first and second solutions come into contact and form magnetic particles.

The invention also relates to a magnetic particle formation kit for use in the above-described method, wherein the kit comprises a first container comprising a first aqueous solution of ferrous and ferric ions and a second container comprising a second basic solution. The composition is chosen such that under the circumstances prevailing in the examination area magnetic particles are formed having good properties for magnetic particle imaging, in particular having eight step change in the magnetisation curve as specified below.

With this administering method, objects can be examined where magnetic particles cannot be introduced in any other manner. For example, this applies to plastic materials or ceramic materials, which could be examined with the method according to the invention for, e.g. hairline cracks. The liquid precursor described above can penetrate such cracks and then form magnetic particles inside the object of examination. The described administering method is also particularly suitable for the examination or measurement of

boreholes or other hollow spaces for visualising and studying porosity or hair cracks in a material.

The invention further relates to an administering composition for administering of a magnetic particle composition into an examination area, comprising  
5 administering particles containing one or more magnetic particles in a first coating material, which first coating material is easily removed in conditions prevailing in the examination area. The advantage of this administering composition is that the magnetic particles are prevented from clumping or agglomerating. The administering composition can be stored in a dry particle powder form, is stable and has a long shelf life. After administering the particles  
10 into the examination area, the coating is removed, for example by dissolving or by degradation, thus removing the restriction for the magnetic particle to move into the examination area and to respond to the external magnetic fields. Preferably, the first coating material is at least partly removed in less than about 20 seconds after administering into the examination area. Suitable first coating materials are polysaccharide or starch.

15 In a special embodiment of the administering composition of the invention, the administering particles comprise only one magnetic particle coated with the first coating material and the diameter of the administering particle is at least 5 times, preferably at least 10 times the diameter of the magnetic particle. The advantage of this embodiment is that the magnetic particles after being released from the administering particle do not easily re-  
20 agglomerate in the examination area.

In yet another embodiment, the administering particles comprise two or more magnetic particles and the two or more magnetic particles are at an average distance of at least 5 times, preferably at least 10 times the average diameter of the magnetic particles. If, the magnetic particles after administering in the examination area are likely to move away  
25 from each other, for example by transport in a flowing medium (bloodstream) or by dilution, a relatively small distance can be chosen, whereas in more static media a distance of at least 10 times the average diameter is preferred.

The magnetic particles in the administering particles can be individually coated with a second coating material different from the first coating material. The  
30 individually coated magnetic particles are embedded in the first coating material. The function of the second coating material preferably differs from the function of the first coating material for example to improve biocompatibility.

Further, it is preferred that the administering particles in the administering composition comprise a further outer coating of a material different from the first or second  
35 coating material. For example, the administering particles comprise an easy dissolvable first

coating material and a more water resistant outer coating material to improve storage stability of the administering composition.

The administering composition can be administered into the examination area directly, directly after dispersing the administering composition in a suitable liquid medium or the administering composition can be pre-dispersed in a liquid to at least partly remove the coating before administering into the examination area. In this method it is preferred that the liquid comprising the at least partly dissolved administering composition is added to the examination area before substantial agglomeration and clumping of the magnetic particles as occurred, typically within about 20 seconds after removal of the coating.

In general, areas of examination comprise any areas where the described administering methods can be introduced. It is also provided that the area of examination is present in the lungs, sinuses or other parts of the breathing system, in the digestive system, inner ears, bladder, vagina, mammary glands, circulation system, particularly the heart, liver, spleen, lymph system; bone marrow and more particularly in inflamed organs and/or tumors.

An alternative embodiment of the present method according to the invention provides that the area of examination may comprise boreholes or materials made of plastic or ceramic.

In addition, the object of examination in which the area of examination is present can comprise a polymer material, especially a thermoplastic polymer, or polymer blend, a polymer melt, a micro-organism, a plant, a plant component, an organism or a portion of an organism.

Basically, the method according to the invention can be used to examine any object, regardless of composition, consistency, form or size. For instance, fluid, viscous and solid objects of examination can be analyzed with the method according to the invention.

For administering magnetic particles to gas filled spaces preferably, aerosol particles are used. The aerosol administering composition is administered for example in the respiratory system or spaces that are difficult to access for investigation, for example cavities or porosity in materials, piping vessels earth formations etc. The invention also relates to an aerosol administering composition for administering of a magnetic particle composition into an examination area, wherein the particles have a diameter below 100  $\mu\text{m}$ , preferably below 10 $\mu\text{m}$ , and wherein the particles are from a hard magnetic material. Preferably, the magnetisation reversal by Neel rotation of the magnetic particles does not take place below 10 mT. With the above aerosol administering composition particles are easily magnetised whilst they are in the aerosol state and are not easily magnetised when absorbed or in contact with the walls surrounding the cavity. The contrast in the magnetic particle imaging

technique is obtained from the difference between the easy magnetisable aerosol particles and the particles that are hindered in geometric rotation and not easily reverse magnetisation in an external magnetic field.

Yet another embodiment of the invention relates to an administering  
5 composition for investigating small vessels, comprising particles having a size at least 8,  
preferably at least 10 micrometer, which particles comprise a magnetic particle and  
optionally a coating material, which magnetic particle and optional coating material slowly  
degrade in the vessels. As the size of these particles is approximately the size of the small  
blood vessels, the particles get stuck and accumulate in the small blood vessels. This provides  
10 information on the presence and perfusion of small blood vessels in certain tissues, for  
example, tumour tissue and lung perfusion. Preferably, the coated particle has a size less than  
150 $\mu$ m more preferred less than 90 $\mu$ m. Preferably, the magnetic particle is a needle shaped  
multi-domain particle, composed of aligned smaller particles wherein the magnetic vectors of  
the smaller particles are largely oriented along the needle axis and which needle shaped  
15 particle degrades to the individual small particles in the vessels. The needles are preferably  
coated, e.g. with albumin, to form a more or less spherical particle. Preferably, the time to  
degrade the particles is at least 10 minutes.

The method according to the invention uses the circumstance that magnetic  
particles that are not saturated can be influenced by an external magnetic field and their  
20 reaction to the external magnetic field can be detected. Conclusions about the environment in  
which the magnetic particles are present can be made in this manner. A reaction to or  
interaction with an applied external field, i.e. magnetic reversal, can be easily generated, with  
a particularly anisotropic magnetic particle, when this particle is not hindered from aligning  
itself in the direction of the external magnetic field lines by, e.g. mechanical, influences. In  
25 how far the behaviour of the magnetic particle in the area of examination is dependent on its  
direct environment can, for example, be precisely detected when this magnetic particle  
changes state or gains/loses movement.

The method according to the invention therefore makes significant use of an  
arrangement as described in the unpublished German patent application, file number 101 51  
30 778.5. For preferred embodiments of this arrangement reference is made to the above patent  
application.

The arrangement used in the invention generates a spatially inhomogeneous  
magnetic field in the area of examination. In the first sub-area, the magnetic field is so weak  
that the magnetization of the particle deviates more or less strongly from the external field  
35 and is therefore not saturated. This first sub-area is preferentially a spatially coherent area; it

can however also be a punctiform area, but also a line or a plane. In the second sub-area (i.e. the rest of the area of examination lying outside the first area), the magnetic field is sufficiently strong to hold the particle in a state of saturation. Magnetization is saturated when the magnetization has aligned almost all particles in approximately the direction of the external magnetic field so that with an increase in magnetic field, the magnetization in that area increases considerably less than in the first sub-area with a similar increase in magnetic field.

By changing the position of the two sub-areas within the area of examination, the (total) magnetization in the area of examination changes. If, therefore, the magnetization in the area of examination or the physical parameters influenced by this are measured, information can be derived about the spatial distribution of the magnetic particles in the area of examination.

To change the spatial position of both sub-areas in the area of examination or to change the magnetic field strength in the first sub-area, an e.g. magnetic field that is localized and/or changes over time can be generated. It is also provided that the signals induced in at least one coil by the change over time of the magnetization in the area of examination are acquired and evaluated to obtain information about the spatial distribution of magnetic particles in the area of examination. The biggest possible signals are achieved by changing the spatial position of both sub-areas as rapidly as possible. A coil, with which a magnetic field can be generated in the area of examination, can be used to acquire the signals. Preferably, at least one separate coil is used.

When changing the spatial position of the sub-area using a magnetic field changing over time, this can induce a similarly periodic signal in a coil. The acquisition of this signal may however be difficult as the signals generated in the area of examination and the magnetic field changing over time are simultaneously effective: it is therefore not possible to differentiate between the signals induced by the magnetic field and the signals induced by the change in magnetization in the area of examination. This can however be avoided in that a magnetic field changing over time acts on a first frequency band on the area of examination and that a second frequency band, which contains higher frequency components than the first frequency band, in the signal received from the coil is evaluated to obtain information about the spatial distribution of the magnetic particles. This exploits the fact that the frequency components of the second frequency band can only be created by a change in the magnetization in the area of examination due to the non-linearity of the magnetization characteristic curve. When the magnetic field changing over time has a sinusoidal periodic behaviour, the first frequency band consists only of a single frequency



component – the sinusoidal fundamental oscillation. In contrast, the second frequency band contains, in addition to this fundamental oscillation, higher harmonics (so-called harmonic waves) of the sinusoidal fundamental oscillation, which can be used for evaluation.

A preferred arrangement for the method in the present invention is characterized in that the means for generating the magnetic field includes a gradient coil arrangement for generating a magnetic gradient field, which reverses its direction in the first sub-area of the area of examination and evidences a zero passage. This magnetic field is – when the gradient coil arrangement e.g. comprises two identical windings carrying opposing flows located on either side of the area of examination (Maxwell coil) – zero at a point on the winding axis and increases almost linearly on both sides of this point with opposite polarities. It is only with these particles located in the area around this field zero point where magnetization is not saturated. For particles outside this area, the magnetization is in a state of saturation.

Therefore an arrangement can be provided with means to generate a magnetic field changing over time and superimposed on the magnetic gradient field for the purpose of moving both sub-areas in the area of examination. The area generated by the gradient coil arrangement is therefore moved around the field zero point, i.e. the first sub-area, within the area of examination by the magnetic field changing over time. With appropriate changes over time and orientation of this magnetic field it is possible to move the field zero point throughout the entire area of examination.

The magnetization change resulting from the movement of the field zero point can be detected by an appropriate coil arrangement. The coil used to detect the signals generated in the area of examination can be a coil that is already used to generate the magnetic field in the area of examination. There are, however, advantages to using a separate coil for reception as this can be decoupled from the coil arrangement producing a magnetic field that changes over time. In addition, an improved signal/noise ratio can be achieved with a coil – and more so with several coils.

The amplitude of the signals induced in the coil arrangement increases proportionally the faster the position of the field zero point changes in the area of examination, i.e. the faster the magnetic field changing over time superimposed on the magnetic gradient field changes. It is however technically difficult to generate a magnetic field changing over time with sufficient amplitude to move the field zero point at the point of the area of examination or with sufficiently large change speed to generate signals with sufficient amplitude. Particularly suitable arrangements for this purpose comprise means to generate a first and at least a second magnetic field superimposed on the magnetic gradient

field, whereby the first magnetic field moves slowly with high amplitude and the second magnetic field moves fast with low amplitude. This generates – preferably by two coil arrangements – two magnetic fields with different speeds and different amplitudes. Another advantage is that the field changes can be so fast (e.g. > 20 kHz) that they lie above the human limit of audibility. It can also be provided that both magnetic fields in the area of examination are generally aligned vertically to one another. This enables the movement of the field-free point within a two-dimensional area. This can be expanded to a three-dimensional area by another magnetic field comprising a component aligned vertically to the two magnetic fields. Another advantage is inherent in an arrangement with a filter downstream of a coil arrangement, which suppresses the signal components in a first frequency band in the signal induced, by the coil arrangement and allows the signal components in a second frequency band, which contains higher frequency components than the first frequency components, to pass. This exploits the fact that the magnetization characteristic curve is non-linear in the area where the magnetization transitions from the non-saturated to the saturated state. This non-linearity has the effect that, e.g. a sinusoidal magnetic field over time with the frequency  $f$  generates, in the area of non-linearity, an induction changing over time with the frequency  $f$  (fundamental oscillation) and integer multiples of the frequency  $f$  (harmonic waves or higher harmonics). The evaluation of the higher harmonics has the advantage that the fundamental oscillation of the magnetic field used to move the field-free point does not have any influence on the evaluation.

It has been found to be effective for some applications, for example for viscosity or flow measurements, that at least a portion of the magnetic particles has anisotropic properties

It can be provided that the magnetic particle is a mono-domain particle whose magnetic reversal is implemented mainly through Brownian rotation or Neel rotation.

In another suitable embodiment of the method according to the invention, the magnetic particle may be represented by a hard or soft magnetic multi-domain particle.

In another embodiment, the magnetic particles comprise hard magnetic materials. It may then be that the hard magnetic materials comprise Al-Ni, Al-Ni-Co and Fe-Co-V alloys as well as barium ferrite ( $\text{BaO} \cdot 6\text{Fe}_2\text{O}_3$ ).

According to another aspect of the method, it is proposed that the material used for encasing or coating can be degraded or dissolved thermally, chemically, bio-chemically, by means of electromagnetic radiation or ultrasound and/or mechanically.

A preferred embodiment provides that the magnetic particles comprise superparamagnetic particles or ferromagnetic particles, particularly in the form of flakes or needles.

According to the present invention, it is provided that the magnetic particles  
5 become saturated when an external magnetic field is applied, especially one with a strength of circa 100 mT or less. Of course, larger saturation field strengths are also suitable for the method according to the invention.

Suitable magnetic field strengths for many applications are circa 10 mT or less. This strength would already be sufficient for many tissue or organ examinations. But it  
10 is also possible to achieve good measurement results with field strengths in the area of 1 mT or less, or circa 0.1 mT or less. For example, concentration data, temperature, pressure or pH values can be determined with high accuracy and resolution with magnetic fields of circa 10 mT or less, circa 1 mT or less and circa 0.1 mT or less.

In the sense of the present invention, an external magnetic field where the  
15 magnetic particles become or are saturated means a magnetic field where circa half the saturation magnetization is achieved.

Suitable magnetic particles here are those that can reach saturation with a sufficiently small magnetic field. A necessary requirement for this is that the magnetic particles have a minimum size or a minimum dipole moment. The term magnetic particle in  
20 the sense of the present invention also comprises particles that can be magnetized.

Suitable magnetic particles favourably have dimensions that are small compared to the size of the voxel whose magnetization is to be determined by the method according to the invention. In addition, the magnetization of the particles should preferably reach saturation at the lowest possible field strengths of the magnetic field. The lower the  
25 field strength required for this is, the higher the spatial resolution capacity or the weaker the (external) magnetic field being generated in the area of examination can be. In addition, the magnetic particles must have the highest possible dipole moment or a high saturation induction so that the change in magnetization produces the largest possible output signals. It is also important for the particles not to be toxic if the method is to be used for medical  
30 examinations.

A preferred form of the present method according to the invention proposes that the magnetic particle is a mono-domain particle that can be reverse magnetized by Neel rotation and/or that the reverse magnetization is caused by Brownian rotation.

Suitable magnetic mono-domain particles are preferably dimensioned so that  
35 only a single magnetic domain (the mono-domain) can be formed in them or Weiß areas are

not present. Suitable particle sizes in a specially preferred embodiment of the present invention lay in the range between 20 nm to ca. 800 nm, where the upper limit is also dependent on the material used. Preferably, magnetite ( $\text{Fe}_3\text{O}_4$ ), maghemite ( $\gamma\text{-Fe}_2\text{O}_3$ ) and/or non-stoichiometric magnetic iron oxides are used as mono-domain particles.

5 In general it is advantageous, especially when a rapid reverse magnetization based on Neel rotation is required, for the mono-domain particles to evidence a low effective anisotropy. Effective anisotropy means the anisotropy resulting from the form anisotropy and the average crystal anisotropy. In the above-mentioned case a change in magnetization direction does not require the particle to be turned. Alternatively, mono-domain particles with  
10 high effective anisotropy can be used when it is desired that the reverse magnetization, when applying an external magnetic field, is implemented by Brownian or geometric rotation. Above all, particles whose reverse magnetization is based on Neel rotation and on Brownian rotation are particularly suitable for viscosity measurements.

Another embodiment of the present method according to the invention  
15 proposes that the magnetic particle may be represented by a hard or soft magnetic multi-domain particle. These multi-domain particles are usually larger magnetic particles in which a number of magnetic domains can be formed. Such multi-domain particles suitably have a low saturation induction.

Hard magnetic multi-domain particles generally have the same magnetic  
20 properties as mono-domain particles with higher effective anisotropy. Soft magnetic multi-domain particles with low saturation magnetization have the advantage that they can be shaped into any form for use in the present method according to the invention. If they have an asymmetrical external form, they are then particularly suitable for local viscosity measurements in the area of examination. Soft magnetic multi-domain particles with high  
25 saturation magnetization must preferably be designed so that the demagnetizing factor becomes small. Both symmetrical and asymmetrical forms can be considered here. For example, a soft magnetic material with high saturation magnetization can be applied as a thin coating on a ball or cube that is not magnetizable. Soft magnetic multi-domain particles with high saturation magnetization that have an asymmetrical form, e.g. in the form of flakes or  
30 needles, can also be used for viscosity measurements.

Therefore, mono-domain particles, where reverse magnetization occurs via Neel and Brownian rotation, are particularly suitable for local viscosity measurements in the area of examination as are soft magnetic multi-domain particles with small or large saturation magnetization that have an asymmetrical external form.

As described above, the magnetic particles also comprise such particles that consist of a non-magnetic core and a coating of a magnetic material. Therefore this comprises in general all magnetic particles that have a low effective anisotropy and those that have a high effective anisotropy. A high coercive force  $H_c$  is necessary in semi-hard and, especially, hard magnets in order to bring the magnetization to zero. Suitably hard magnetic materials comprise Al-Ni, Al-Ni-Co and Fe-Co-V alloys as well as barium ferrite ( $BaO \cdot 6xFe_2O_3$ ).

In general the magnetic particles in the magnetic particle administering composition, are chosen such that good magnetic particle images, in particular a good resolution can be obtained in a given field gradient. In unpublished German patent application number 101 51778.5 a magnetic particle imaging method is described. It is generally described that magnetic mono-domain particles having a size between 20 and 800 nanometres or a glass bead coated with a magnetic coating can be used in this method. However, in order to achieve a good magnetic imaging contrast and resolution at relatively low magnetic field gradients, improved magnetic particle compositions are highly desirable. The inventors have found magnetic particles having improved magnetic particle imaging properties.

Preferably, the magnetic particles in the magnetic particle administering composition have a magnetization curve having a step change, the step change being characterized in that the magnetization change, as measured in an aqueous suspension, in a first field strength window of magnitude  $\Delta$  around the inflection point of said step change is at least a factor 3 higher than the magnetization change in the field strength windows of magnitude  $\Delta$  below or in the field strength windows of magnitude  $\Delta$  above the first field strength window, wherein  $\Delta$  is less than 2000 microtesla, preferably less than 1000 microtesla, and wherein the time in which the magnetisation step change is completed in the first  $\Delta$  window is less than 0.01 seconds, preferably less than 0.005 sec, more preferably less than 0.001, most preferably less than 0.0005 seconds. It has been found, that such magnetic particles are particularly suitable for magnetic particle imaging, in particular for obtaining a good resolution of the image. It is further preferred, that the magnetic particle composition has a magnetisation curve, wherein the step change is at least 10%, preferably at least 20 %, more preferably at least 30 % and most preferably at least 50% of the total magnetisation of the particle composition as measured at an external magnetisation field of 1 Tesla. It is further preferred, that the magnetization change in the first field strength window of magnitude  $\Delta$  around the inflection point of said step change is at least a factor 4, preferably at least a factor 5 higher than the magnetization change in the field strength

windows of magnitude delta below or in the field strength windows of magnitude delta above the first field strength window.

The magnetic particle composition is particularly useful for use in a magnetic particle imaging technique. The particles show good spatial resolution at relatively low field strength gradients. Further, the magnetic particle composition allows for a relatively high scanning speed for examining a large examination area. For example, for application in medical magnetic particle imaging, where the step change occurs preferably at a delta value below 1000 microTesla, the particle composition has a resolution value better than between 0.1 and 10 mm at magnetic field strength gradients between 10 and 0.1 T/m. With the magnetic particle imaging technique using the magnetic particle compositions according to the invention extremely good resolution can be obtained, for example in a range from 0.1 to 10 micrometres in applications, where are very high magnetic field is gradients can be achieved, for example in microscopy. It is noted that strictly speaking, magnetic field strength is expressed in H (A/m). However, in the present application, when reference is made to magnetic field strength, B-fields are meant. A magnetic fields B of 2000  $\mu$ T as described above corresponds to an H field of  $2 \text{ mT}/\mu_0 = 1.6 \text{ kA/m}$ , that is the equivalent H field that would produce a B field of 2 mT in vacuum.

A method for measuring the magnetisation curve and the required step change is as follows. A sample of a magnetic particle composition is suspended in water, optionally with the help of a simple detergent. To prevent clumping and/or to de-agglomerate the magnetic particles an ultrasound treatment possible can be used. The concentration of the magnetic particle composition is less than 0.01gr core mass per liter of solvent. With core mass is meant the mass of the magnetic material in the magnetic particle composition. The suspension is brought into a fast magnetometer. (i.e. a device that measures the magnetization of the sample while an external field is applied). Suitable fast magnetometers are known to the expert. The magnetometer is equipped with means allowing to produce an external field at the sample position in at least two orthogonal directions simultaneously, i.e. to produce any magnetic field below a given maximum amplitude and a given maximum speed of change. The magnetisation is measured also in at least two orthogonal directions in the same plane.

First the saturation magnetisation is measured. For this, a magnetic field of about one Tesla is applied in one direction and the magnitude of magnetization is measured after at least 10 seconds. Then the measurement sequences for determining the step change starts. The sequence starts with choosing a field vector with an external field magnitude below 20mT. This field is applied for at most 100 seconds. Then a second direction is

chosen. This direction defines the scalar values of the field  $H$  and the magnetization  $M$ . The field is rapidly changed, preferably less than 1 millisecond, so that it lies now in  $-H$  direction with some magnitude below 20 mT. Then the field is changed from  $-H$  to  $+H$  e.g. in a linear way and the (now scalar i.e. projected) magnetization is recorded. The magnetization curve is recorded in less than 0.01s but longer than  $1\mu\text{s}$ . Where the magnetisation curve shows a step change, a first window of size  $\delta$  is positioned centrally on the inflection point of the magnetisation step change. Similarly, a window of size  $\delta$  is positioned below and above the first window, and the required step change is evaluated by determining the change in magnetisation in each of the windows.

Whether or not a given magnetic particle composition has the required step change depends in a complicated way on many variables, for example of the size of the particles, the particle size distribution, the shape of the particles, the damping constant for Neel rotation, the type of magnetic material, the crystallinity and the stoichiometry of the composition of the magnetic material. It has been found that it is particularly important that the particle size distribution of the particle composition is narrow. Preferably, the magnetic particle composition according to the invention has a narrow particle size distribution wherein at least 50 weight % of the particles have a particle size between plus or minus 50%, preferably 25%, more preferably 10% of the average particle size. Preferably, the amount of particles within the specified windows, is at least 70 wt %, preferably at least 80 wt %, and most preferably at least 90 wt %. Particularly good results are obtained with mono-domain particles have a low magnetic anisotropy with a field needed for inducing Neel rotation of substantially below 10mT, preferably below 5 mT, more preferably below 2 mT. Preferably, the magnetic particles are mono-domain particles having an average particle size between 20 and 80 nanometres, more preferably between 25 and 70 nanometres, must preferably between 30 and 60 nanometres, wherein at least 50, preferably at least 60, more preferably at least 70 weight % of the particles have a particle size between the average particle size plus or minus 10 nanometre.

In an alternative embodiment of the magnetic particle composition according to the invention, the magnetic particle is a multi-domain particle having substantially a needle shape having a demagnetisation factor of less than 0.001. This magnetic particle composition is particularly useful in non-medical applications where the needles shape is not a disadvantage. In another alternative embodiment, the magnetic particle composition according to the invention comprises magnetic particles comprising a non-magnetic core covered with a magnetic coating material, wherein the thickness of the coating is between 5 and 80 nanometres and wherein the demagnetisation factor is less than 0.01 and a diameter

below 300 $\mu$ m. Also in these alternative embodiments it is advantageous to have a small particle size distribution as described above. The physical parameters of the magnetic particles in these embodiments are preferably chosen to meet the step change requirement as described above for achieving good imaging properties.

5                   The magnetic particle composition according to the invention can be manufactured by first forming magnetic particles, for example by precipitation, for example by contacting a solution comprising ferrous and ferric ions with a solution comprising sodium hydroxide as described above. In principle, a known precipitation process can be used. It is also possible to grind the particles from bulk material, for example using a high  
10 speed ball mill. The essential next step for obtaining a good magnetic particle composition is the selection and separation of the particles. The first step is to perform a size selection process by filtering and/or centrifuge methods. The next step is to perform a selection process based on the magnetic properties of the particles, for example, using oscillating magnetic gradient fields.

15                   The present invention is based on the surprising recognition that numerous administering forms can be used for the magnetic imaging methods described here using magnetic particles in a gradient magnetic field, whereby the method permits a specific magnetic particle administering form for every analysis task.

20                   The characteristics of the invention described above and in the claims can be used both individually and in any combination for the implementation of the invention in its various embodiments.